

REMARKS

Status of the Claims

Claims 1-15 were pending as shown above and claims 2-5 were under active examination. By amendment herein, claim 2 has been amended to clarify the steps of obtaining the polynucleotides of the array. *See, e.g.*, pages 26-28; 31-33; Example 1. Claims 3-5 have also been amended for proper dependency on amended claim 2. As the amendments clarify the issues for appeal, entry after final is appropriate. Thus, claims 2-5 are pending as shown above.

Drawings

In response to notice that the drawings were not acceptable, Applicants are employing the services of a competent draftsperson and will submit corrected drawings under separate cover.

Notice of Non-Compliant Amendment

In the continuation sheet of the Notice of Non-Compliant amendment, it was asserted that Applicants did not fully respond to the assertions raised in paragraph 7, paragraphs 12 and 13 and page 12 of the Final Office Action or that Applicants' responses were unpersuasive.

While Applicants submit that the Examiner may not have been persuaded by the previous arguments, all the issues were properly addressed and the response after final was not non-compliant on the grounds that rejections were not addressed. Nonetheless, Applicants have included separate sections below regarding the arguments specifically culled out in the Notice of Non-Compliant Amendment.

35 U.S.C. § 112, 1st paragraph, written description

Claims 2-5 were again rejected under 35 U.S.C. § 112, 1st paragraph as allegedly containing new matter for reciting an array of polynucleotides "consisting of accessible regions of cellular chromatin." (Final Office Action, paragraph 6). In addition, claims 2-5 were again rejected for allegedly failing to describe the steps that are used to isolate the polynucleotide sequences and that the claimed arrays can encompass any "available" nucleic acids. (Final Office Action, paragraphs 8-14). In addition, *Fiers v. Revel* was again cited as allegedly

establishing lack of description of the claimed arrays. (Final Office Action, paragraphs 15-17). The rejection is premised on the alleged failure to actually prepare an array in the disclosure.

Applicants reiterate that written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981); *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). Working examples of multiple representative species are also never required to show possession. *Id.* See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981).

In the instant case, the evidence of record establishes that making an array was well known to the skilled artisan. Therefore, it does not need to be exemplified in the as-filed specification in order to be adequately described. Satisfaction of the written description requirement necessitates that subject matter which is novel be described – in this case preparation of polynucleotide sequences such that each polynucleotide comprises an accessible region of cellular chromatin.

Furthermore, the facts of the instant case are entirely unlike those in *Fiers*. In that case, the claims were directed to particular DNA molecules whereas in the pending case, the claims are directed to arrays that must necessarily comprise a plurality of necessarily different polynucleotide sequences. In other words, it is a different matter to claim a DNA molecule (as in *Fiers*) than it is to claim an array made up of polynucleotides comprising accessible regions, as claimed. As the polynucleotides of the array can and will differ tremendously from each other and between arrays, the written description requirement is satisfied if the specification describes that which is new, namely how to generate and isolate polynucleotides of accessible regions that can be formed into arrays.

Thus, the specification clearly describes the claimed subject matter. For the reasons of record, adequate description is present in the original claims and description; therefore the written description requirement has been satisfied. Applicants have shown possession of the claimed arrays at the time of filing – clearly and unmistakably. Therefore, the rejection should be withdrawn.

New argument addressing paragraph 7 of the Final Office Action

In paragraph 7 of the Final Office Action, it was asserted that the sequence listing “has been found to comprise but a single sequence.”

Applicants again note that this rejection was raised previously in an Office Action dated May 28, 2008 and addressed in a Response filed August 28, 2008. As indicated in the Final Office Action mailed February 26, 2009, all the rejections were withdrawn in view of Applicants’ arguments.

Nonetheless, Applicants reiterate satisfaction of the written description requirement does not necessitate that the specification set forth the sequence of every single nucleic acid by structure in the specification. See, *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). Working examples of multiple representative species are also never required to show possession. *Id.*

Furthermore, SEQ ID NO:1 as cited on page 7 of the Office Action is not the sequence of an accessible region – it is the sequence of a zinc finger protein that can bind to such accessible regions. As disclosed in the Examples, approximately 40,000-50,000 clones corresponding to accessible regions were actually generated. See, page 62, line 29 of the specification.

Furthermore, 405 of these clones were further analyzed in a variety of ways. See, Example 2. The written description in this case does not require a listing of the precise sequence of any of the accessible region-containing clones. Rather, all that is required is that the specification evince possession of the polynucleotides forming the claimed arrays. In this case, the specification more than amply meets this requirement in explicit disclosure of a multitude of polynucleotides corresponding to accessible regions.

Thus, the fact that the sequence listing does not include exemplary sequences of accessible regions is not germane to the written description inquiry.

New argument addressing paragraphs 12 and 13 of the Final Office Action

In paragraphs 12 and 13 of the Final Office Action, it was asserted that the “specification has not been found to provide an adequate written description of those nucleic acid molecules that are useful versus those that not” and “the absence of an adequate written description for any

such array does not reasonably suggest that applicant had possession of the array" at the time of filing.

In response, Applicants note that all accessible regions isolated and placed on an array as claimed are useful, for example in screening. Thus, Applicants statement that the polynucleotides can and will differ tremendously from each other and between arrays is no way negates satisfaction of the written description requirement. While accessible regions from different regions of the genome (and/or from different cell types) will inevitably have different sequences, they are all useful sequences and are fully described in the as-filed specification, both in terms of how to isolate them and how to place them on an array, and in terms of how to use them.

Furthermore, Applicants traverse the assertion that there is "an absence of adequate written description." If the Examiner is referring to an alleged absence of working examples in the form of particular sequences or arrays, it is again noted that working examples are never required to satisfy the written description requirement. See, *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). The claimed arrays are more than adequately described by the Examples and the detailed description, which describe how to isolate accessible regions and how to place them on array as claimed.

35 U.S.C. § 112, 1st paragraph, enablement

Claims 2 to 5 were again rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the as-filed specification. (Final Office Action, paragraphs 24-27).

To the extent that the foregoing amendments do not obviate the rejection, Applicants strongly traverse the Examiner's assertion that "none of the examples is directed to the identification of nucleic acid molecules that correspond to accessible regions of cellular chromatin." (Final Office Action, page 12). In fact, the examples clearly depict identification of polynucleotide sequences corresponding to accessible regions by the claimed steps, namely by enzymatic digestion of cellular chromatin, deproteinization of digested chromatin and further enzymatic digestions of the deproteinized fragments to generate polynucleotide sequences that correspond to accessible regions of cellular chromatin. *See, e.g.*, Examples 1 and 2.

Moreover, attaching these sequences to distinct addresses on a solid support to form an array is not unpredictable as asserted by the Examiner. (Final Office Action, page 15). The passage the Examiner refers to in Jones (U.S. Patent No. 5,858,671), relates to enzymatically synthesizing oligonucleotides (by repeated couplings) onto solid substrates to form an array. This is entirely unlike the claimed arrays in which already isolated (not synthetic) polynucleotide sequences are attached to a solid support at discrete addresses using routine and predictable techniques (see, e.g., U.S. Patent No. 6,600,031; 6,326,489; 6,548,021 and WO 02/18648 cited on page 52 of the specification) known to the skilled artisan at the time of filing and set forth in the specification.

For the reasons of record and reiterated herein, any experimentation needed to make and use the claimed arrays is routine in view of the teachings of the specification and the state of the art. Thus, the Office has not provided sufficient evidence supporting non-enablement and, in the absence of necessary relevant evidence contradicting the teachings of the specification and state of the art, the rejection cannot be maintained.

New argument addressing page 12 of the Final Office Action

In the Notice of Non-Compliant amendment it was asserted that while Applicants responded to the Examiner's rejections as set forth on page 12 of the Final Office Action, the arguments were apparently unpersuasive (Non-Compliant Amendment, continuation sheet):

At page 12 of the Office Action, the issue of the specification not enabling the use of the arrays of DNA comprising "accessible regions" in any method that has utility under 35 U.S.C. § 101 was developed. While applicant does address the enablement-based rejection as it pertains to the making of the arrays, it has not been found to enable the use of arrays in any method that has utility under 35 USC 101, when as noted above, "the polynucleotides of the array can and will differ tremendously from each other and between arrays."

Applicants note that it is acknowledged the rejection was addressed, thus complying with the requirements in responding to an Office Action. Nonetheless, it is again noted that all accessible regions isolated and placed on an array as claimed are useful, for example in screening (e.g., ChIP on a chip). Again, Applicants statement that the polynucleotides can and will differ

tremendously from each other and between arrays is no way negates satisfaction of the enablement and/or utility requirement(s). While accessible regions from different regions of the genome (and/or from different cell types) will inevitably have different sequences, they are all useful sequences and the as-filed specification fully enables the skilled artisan to make and use these arrays.

35 U.S.C. § 101/112

Claims 2 to 5 were also rejected under 35 U.S.C. § 101 and § 112 on the grounds that the claimed invention is not supported by a specific, substantial and credible (or well-established) utility based on the assertion that not all nucleic acids have utility. (Final Office Action, paragraphs 28-33). In response to Applicants' previous arguments, it was asserted that the utilities set forth on page 53 are "not deemed specific to the members of the array." (Final Office Action at page 17).

Applicants traverse the assertion that the utilities set forth in the specification are not "specific to the members of the array." To the contrary, the specification (*e.g.*, Section entitled "Applications" beginning on page 55) sets forth uses of the arrays that are specific to the fact that the claimed arrays include sequences of accessible regions, for example, making ChIP on a chip analysis possible for the first time (see, page 56, lines 8-16):

The methods described herein allow the isolation, from among the large amount of intergenic DNA in the human genome, of only those sequences which serve a regulatory function; thereby making it possible, for the first time, to prepare a microarray of human regulatory sequences. In addition to intergenic regulatory sequences, regulatory sequences located within genes are also obtained. Accordingly, the arrays produced as described herein make possible "ChIP on a chip" to identify the direct *in vivo* targets, in the human genome, of any regulatory factor of interest. Moreover, and in contrast to previous methods, all binding detected in a ChIP assay, and further analyzed (by ChIP on a chip) using a regDNA array, is relevant to regulation.

This is only one of several specific utilities set forth in the specification and is clearly "specific" to the claimed arrays. Additional utilities are set forth in detail in the specification, for example on pages 55-61. These utilities includes identification of regulatory proteins,

identification of DNA-binding proteins, RegDNA chip profiling, chromatin epigenome profiling, toxicity profiling, SNP interrogation, microRNA validation, drug discovery, expression profiling, etc. These utilities are clearly credible (as well as substantial and specific). Moreover, they are well-established utilities.

Furthermore, the presence of a well-established utility is sufficient to meet the utility requirements of 35 U.S.C. § 101/112. Applicants submit that, although they need only satisfy one of these two alternatives, they have provided both specific, credible and substantial utilities, as well as a well-established utility, for the arrays as claimed.

It appears that the Examiner will not consider a utility for the claimed arrays in the absence of working examples regarding the arrays *per se*. If this were the standard, the concept of “well known” utility would be meaningless. Applicants submit that they have provided credible, specific and substantial utility, as well as a well-established utility, for the arrays of the present invention.

Based on the foregoing, applicants respectfully submit that the rejections under 35 U.S.C. §101, for lack of utility, should be withdrawn.

35 U.S.C. § 112, 2nd paragraph

Claims 2-5 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting “accessible regions.” (Final Office Action, paragraphs 39-40). In response to Applicants’ arguments, it was asserted that the “claims seemingly encompass nucleic acids that in one case may be non-accessible, yet under evaluation from a different tissue type and/or organism (or reaction condition), may now be construed as being accessible.” (Final Office Action, page 21).

Applicants again note that the claims are definite in that it is plain that the accessible regions of the array are identified with respect to the starting cellular chromatin. Thus, it is clear to the skilled artisan what is meant by this particular claim term. *See, e.g., In re Marosi*, 218 USPQ 289 (Fed. Cir. 1983). Furthermore, the definition of “accessible region” found at page 12, line 26 to page 13, line 29 is not “exemplary,” but, rather, plainly sets forth that accessible regions of cellular chromatin are any regions of chromatin that are not bulk chromatin and that a probe used to determine if a region is accessible is any enzyme or chemical that has altered

reactivity with accessible chromatin as compared to bulk chromatin. See, also, page 24, line 29 to page 25, line 8 of the as-filed specification:

The accessibility of DNA in chromatin refers to any property that distinguishes a particular region of DNA, in cellular chromatin, from bulk cellular DNA. See, for example, Wolffe “Chromatin: Structure and Function” 3rd Ed., Academic Press, San Diego, 1998 for a description of cellular chromatin. For example, an accessible sequence (or accessible region) can be one that is not packaged into nucleosomes, or can comprise DNA present in nucleosomal structures that are different from that of bulk nucleosomal DNA (e.g., nucleosomes comprising modified histones). An accessible region includes, but is not limited to, a site in chromatin at which an enzymatic (e.g., DNaseI) or chemical probe reacts, under conditions in which the probe does not react with similar sites in bulk chromatin. Such regions of chromatin can include, for example, a functional group of a nucleotide, in which case probe reaction can generate a modified nucleotide, or a phosphodiester bond between two nucleotides, in which case probe reaction can generate polynucleotide fragments or chromatin fragments.

Attention is also directed to co-owned U.S. Patent Nos. 7,217,509; 7,097,978; and 7,001,768 and 6,511,808, which show how the term “accessible regions” was used in the art at time of filing.

Therefore, in light of the specification and art as a whole, the skilled artisan would clearly be apprised as to the metes and bounds of the claims. Accordingly, the rejection cannot be sustained.

35 U.S.C. § 102(b)

Claims 2 to 5 were again rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 6,153,379 (hereinafter “Caskey”) which was cited for teaching arrays of synthesized oligonucleotide primers ranging from about 7 to about 30 nucleotides in length. (Final Office Action, paragraphs 43-45). The Examiner also asserted that Caskey’s statement that their array includes “oligonucleotide primers comprising all possible N-mers” was “deemed to meet a limitation of each of claims 2-5.” *Id.*

Applicants traverse the rejection and supporting remarks.

The pending claims are drawn to polynucleotide-including arrays in which each

polynucleotide of the array comprises a sequence of an accessible region of cellular chromatin. In addition, the polynucleotides of the array are 100-300 base pairs in length. By contrast, Caskey's arrays do not consist of accessible region sequences. Nor are Caskey's oligonucleotides between 100 and 300 base pairs in length. Therefore, because Caskey does not disclose all the elements of the claims and because the evidence or record clearly establishes that the recited process steps impart structural limitations that distinguish the claims from the arrays of the cited reference, Caskey cannot anticipate any of the pending claims and withdrawal of the rejection is in order.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that all of the pending claims are in condition for allowance and request early notification to that effect.

Should the Examiner have any further questions, Applicants request that the undersigned be contacted at (650) 493-3400.

Respectfully submitted,

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